Integrated circulating tumor DNA and cytokine analysis for therapy monitoring of *ALK*-rearranged lung adenocarcinoma

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Background & objectives

Approximately 3-7% of non-small cell lung cancers harbor a structural rearrangement in the *ALK* gene (ALK+ NSCLC) resulting in the constitutive activation of the translated protein. The development of ALK inhibitors for targeted therapy has improved the prognosis of ALK+ NSCLC patients. However, treatment resistance eventually develops, commonly through the emergence of secondary *ALK* resistance mutations and other acquired alterations. Close monitoring of therapy success or failure is thus critical for patient management. While tumor re-biopsies could detect the emergence of clinically relevant tumor clones, these procedures are associated with risks that preclude their use in many cases. Detection of circulating tumor DNA (ctDNA) in biological fluids is a minimally invasive alternative to tissue biopsy for therapy monitoring. Cytokines are released in the tumor microenvironment to influence inflammation and tumorigenic mechanisms, and serum cytokine levels have been associated with the risk for tumorigenesis in various cancers such as lung, ovarian, breast, and colorectal carcinomas. We investigated the potential biomarker utility of circulating cytokines vis-à-vis ctDNA in ALK-rearranged+ lung adenocarcinoma (ALK+ NSCLC) and explored the optimal combination of molecular parameters that could indicate disease progression.

Methods

Longitudinal serum samples (n=296) were collected from ALK+ NSCLC patients (n=38) under tyrosine kinase inhibitor (TKI) therapy and assayed to quantify eight cytokines: IFN-γ, IL-1β, IL-6, IL-8, IL-10, IL-12p70, MCP1, and TNF-α. Generalized linear mixed-effect modeling was performed to test the performance of different combinations of cytokines and previously determined ctDNA parameters in identifying progressive disease.

Results

Serum IL-6, IL-8 and IL-10 were elevated at progressive disease, with IL-8 having the most significant impact as a biomarker. Integrating changes in IL-8 with ctDNA parameters maximized the performance of the classifiers in identifying disease progression, but this did not significantly outperform the model based on ctDNA alone.

Conclusion

Serum cytokine levels are potential disease progression markers in ALK+ NSCLC. Further validation in a larger and prospective cohort is necessary to determine whether the addition of cytokine evaluation could improve current tumor monitoring modalities in the clinical setting.